Distinct temporal patterns of T cell receptor signaling during positive versus negative selection in situ.

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Public Summary:
During T cell development, the T cell receptors found on the surface of immature thymocytes (T cell precursors) are screened for their ability to recognize peptide-bound major histocompatibility complexes, a process known as positive selection. Additionally, autoreactive thymocytes are eliminated by negative selection to produce a protective, yet self-tolerant, repertoire of T cells. One widely held model of thymocyte selection posits that weak T cell receptor signals promote thymocyte survival and differentiation, whereas stronger signals lead to deletion of the cells by negative selection. Here, we used two-photon microscopy to define T cell receptor signaling during thymocyte selection within intact thymic tissue under conditions that preserved the dynamic migration of thymocytes and their interaction with thymic cells. We found that negative selection was associated with prolonged T cell receptor signaling and stable cellular interactions, whereas positive selection involved surprisingly brief and infrequent T cell receptor signals. We also investigated the contributions of the type of peptide-presenting cells, costimulatory signals, and ligand potency to the pattern of T cell receptor signaling. Our data shed light on how different components of the thymic micro-environment contribute to temporal TCR signaling patterns during positive and negative selection.

Scientific Abstract:
The recognition by the T cell receptor (TCR) of self-peptides presented by the major histocompatibility complex (MHC) on antigen-presenting cells, such as dendritic cells and thymic epithelial cells, controls T cell fate in the thymus, with weak TCR signals inducing survival (positive selection) and stronger signals inducing death (negative selection). In vitro studies indicate that peptide ligands that induce positive selection stimulate a low, but sustained, pattern of TCR signaling; however, the temporal pattern of TCR signaling in MHC class I-restricted thymocytes (thymocytes that are presented with peptides by MHC class I) in the thymus, under conditions that support positive selection, is unknown. We addressed this question by examining intracellular Ca(2+) dynamics and migratory changes in thymocytes undergoing positive and negative selection in thymic slices. Brief, serial signaling events that were separated by migratory periods and low cytosolic Ca(2+) concentrations correlated with the positive selection of MHC class I-restricted thymocytes, whereas sustained Ca(2+) signaling and the arrest of thymocytes were associated with negative selection. Low-avidity peptides and the presentation of peptides by cortical thymic epithelial cells, rather than dendritic cells, failed to induce strong migratory arrest of thymocytes, which led to transient TCR signaling. Thus, we provide a comparison of positive and negative selection signals in situ and suggest that the absence of strong stop signals distinguishes between positive and negative selection.